UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,325	06/02/2005	Michihiro Ohno	HIR-05-1144	3199

35811 7590 05/10/2006

IP GROUP OF DLA PIPER RUDNICK GRAY CARY US LLP
1650 MARKET ST
SUITE 4900
PHILADELPHIA, PA 19103

EXAMINER	
HABTE, KAHSAY	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 05/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/537,325	OHNO ET AL.	
	Examiner	Art Unit	
	Kahsay Habte	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 17-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 17-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-11 and 17-21 are pending in this application.

Response to Amendment

2. Applicant's amendment filed 05/01/2006 in response to the previous Office Action (02/01/2006) is acknowledged. The obviousness-type double patenting rejection of claims 1-11 and 17 has been maintained. Upon further review of the case, it is deemed necessary to raise new issues that need further rejection. Applicant's amendment also raises new issues that need further rejection.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-11 and 17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5-13 of U.S. Patent No. 6,407,096. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is significant overlap between the claims of U.S. Patent No. 6,407,096 and the claims of the instant application. The overlap arises when formula (II) in claim 1 of the U.S. Patent No. 6,407,096 has the following substituents: A^3 = alkylene, alkenylene or alkynylene; R^1 = X-(CH_2)n-$COOR^5$ (equivalent to R^4 in formula (I) of the instant application); R^3 = hydrogen, halogen, alkyl or alkoxy; A^1 = O; m = 1; A^2 = N-CH_2-; A^4 = NR^5CO; R^2 = phenyl, naphthyl or alkyl (equivalent to R^1 in formula (I) of the instant application).

Response to arguments

Applicant's argument filed 05/01/2006 has been fully considered but it is not persuasive.

Applicants argue that the obviousness-type double patenting rejection over U.S. Patent No. 6,407,096 ("Ohtake") indicating that the activity of the claimed species show unexpected effect over Ohtake. Applicants also argue the obviousness-type double patenting rejection by citing a case law: *In re Kaplan*, 229 USPQ 678 (Fed. Cir. 1986). In regard to the argument, "[t]hose having the amide structure set for the in independent claims 1 and 17, would have a dramatically increased and advantageous effect on platelet aggregation over the broad genus of compounds claimed in Ohtake. The marked increase in activity of this species, as described and claimed in this application, represent an unexpected and surprising result over the genus of Ohtake", applicants have to provide a declaration under oath that shows said advantageous effect on platelet aggregation.

Applicants argue, "[t]he subject matter claimed in Ohtake may overlap the subject matter presently claimed when A^3, R^1, R^3, A^1, A^2 and A^4 are all assumed to be specific groups. There fore, this is a case of 'domination' controlled by the decision of *In re Kaplan*, 229 USPQ 678 (Fed. Cir. 1986). A case of domination occurs when an earlier patent includes broad or generic claims which read on an invention defined by a later patent (or application) having narrower or more specific claims." The examiner disagrees with applicants. This is not relevant to In *re Kaplan*, since the claimed invention is not different from the Ohtake. There is overlap of subject matter between

Ohtake and the instant claims as admitted by applicants. In *re Kaplan*, the process claim deal with the issue of a single solvent vs. mixture of solvents. *In re Kaplan* deals with a process of making alkane diols and triols *in the presence of an organic solvent.* Among organic solvents disclosed and specifically claimed in the Kaplan patent are known as "tetraglyme" (in more explicit nomenclature, dimethyl ether of tetraethylene glycol) and sulfone. Two of the Kaplan dependent claims (10 and 11) individually name these specific solvents, respectively. In *re Kaplan*, the solvent mixture was not claimed. This is not the situation here. Note that *In re Kaplan* unlike this case is not a "domination" case. Applicants are claiming compounds that fall within the genius of Ohtake. Applicants can overcome this rejection, by filing terminal disclaimer or by showing unexpected effect under oath.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. A method of treating or preventing thrombosis or diseases accompanying thrombus (claim 18) wherein the thrombosis is in coronary arteries, in cerebral arteries,

in peripheral arteries, or in peripheral veins coronary arteries (claim 19) and wherein the disease is selected from myocardial infraction, unstable angina, cerebral infarction, transient ischemic attack, or peripheral arterial occlusive disease (claim 20), but the specification is not enabled for such a scope.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The scope of the claims is not adequately enabled solely based on the platelet aggregation inhibitory activity provided in the specification. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Test procedures and assays are provided in the specification at page 57 only for 11 compounds and it is concluded that the representative compounds of formula (I) demonstrated positive inhibitory activity with IC_{50} ranging from 5.3 nM to 55 nM, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced the instant claims. The disorders encompassed by the instant claims (e.g. treating or preventing thrombosis in general), some of which have been proven to be extremely difficult to treat. There is no reasonable basis for assuming that the myriad of

compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Thrombosis is an obstruction of an artery or vein by a blood clot (thrombus). Arterial thrombosis is generally more serious because the supply of oxygen and nutrition to an area of the body is halted. Thrombosis of one of the arteries leading to the heart (heart attack; see infarction) or of the brain (stroke) can result in death and, in a vessel of the extremities, may be followed by gangrene. Acute arterial thrombosis often results from the deposition of atherosclerotic material in the wall of an artery, which gradually narrows the channel, precipitating clot formation. A thrombus that breaks off and circulates through the bloodstream is called an embolus. Infarction is a blockage of blood circulation to a localized area or organ of the body resulting in tissue death. Infarctions commonly occur in the spleen, kidney, lungs, brain, and heart. The acute emergency known as myocardial infarction, or heart attack, is usually caused by a blockage in one of the coronary arteries that supply blood to the heart muscle. The blockage typically occurs when a blood clot (see thrombosis) lodges in an area already narrowed by arteriosclerosis; other causes are vasospasms in the arterial walls or viral infection of the heart. Symptoms include a crushing pain in the chest radiated to either arm (more commonly the left arm), the jaw, and the neck, although in some cases there are no symptoms at all. The seriousness of the infarction is dependent upon the

amount of heart muscle affected, how long the area is deprived of blood, and whether it affects the natural pacemaker of the heart, setting off arrhythmias such as ventricular fibrillation. Death of heart muscle tissue and heart failure may result (see congestive heart failure); damage to other vital organs, including the brain, may occur if the heart is unable to pump necessary oxygen and blood to them

Hemophilia is a genetic disease in which the clotting ability of the blood is impaired and excessive bleeding results. The disease is transmitted through females but almost invariably affects male offspring only. A male born to a carrier mother has a 50% chance of having the disease. A hemophiliac cannot pass the disease to his sons, but all his daughters will be carriers. There are two diseases usually classified as hemophilia: hemophilia A (classical hemophilia, or Factor VIII deficiency) and hemophilia B (Christmas disease, or Factor IX deficiency). Small wounds and punctures are usually not a problem for hemophiliacs and can be treated as in a nonhemophiliac. Uncontrolled internal bleeding, however, can result in pain and swelling and permanent damage, especially to joints and muscles. The symptoms often first appear in toddlers as their joints begin to bear weight.

According to page 3421 of a review article by Jonathan Gibbins *Journal of Cell Science* 117 (16), pp. 3415-3425, 2004, "The biggest challenge presented to researchers studying platelet biology is to relate the significance of platelet signaling and function in vitro to the in vivo situation of haemostasis and thrombosis. The use of in vivo models of thrombosis, as well as sophisticated methodology to measure platelet

signaling and thrombus formation under flow, are important technical development toward this aim." This shows that the study is at its early stage and that further study is needed to understand the basic mechanism of platelet aggregation and thrombus formation.

In regard to the "method of preventing thrombosis", to this day the only means available is the treatment of some forms of thrombosis, but not the prevention of thrombosis.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

6. Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In claim 21, it is recited a method of inhibiting or preventing platelet aggregation, but the specification is not enabled for such a scope.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The scope of the claims is very broad. It covers the prevention or inhibition of platelet aggregation in any subject that may or may not need the inhibition of platelet aggregation. See details above in 5. It is recommended that applicants delete this claim.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 5, the phrase "R^1 is unsubstituted phenyl, furyl, thienyl, or pyridyl, or phenyl, furyl, thienyl, or pyridyl substituted with one.." is not clear. Are phenyl, furyl or thienyl permitted to have one of plurality of substituents recited in (a) to (o)? If so, the claim should be written in such way to avoid ambiguity.

There should be a semi colon to separate the unsubstituted phenyl, furyl, thienyl, or pyridyl from the substituted ones. It is recommended that applicants amend the claim as "R^1 is unsubstituted phenyl, furyl, thienyl, or pyridyl; or R^1 is substituted phenyl, furyl, thienyl, or pyridyl with one..". to overcome this rejection. The same correction is required in claims 6-10.

Claim Objections

8. Claim 5 is objected to under 37 CFR 1.75(c) as being in improper form because claim 5 is multiply dependent on claims 4 and 1. See MPEP § 608.01(n).

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kahsay Habte
Primary Examiner
Art Unit 1624

KH
May 9, 2006